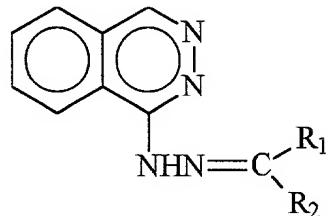


1 I claim

2 1. A method of improving the stability of a hydralazine composition during  
3 manufacturing or storage comprising coupling an N-protecting group with hydralazine to  
4 produce a compound having the formula:

5

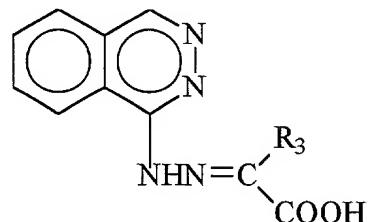


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7

8 or a compound having the formula:

9



10

11

12 where R<sub>1</sub> and R<sub>2</sub> are independently H, substituted or unsubstituted branched or straight  
13 chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl,  
14 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
15 unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form part of a  
16 substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms;  
17 where R<sub>3</sub> is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,  
18 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or  
19 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group  
20 having the formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 1 to about 7; and

1 wherein said N-protecting group is removed from said compound after manufacturing or  
2 storage.

3

4 2. The method of Claim 1 wherein the N-protecting group is acid-labile and is removed  
5 from the hydralazine prior to administration of said compound to a patient.

6

7 3. The method of Claim 2 wherein the N-protecting group is plasma-labile and is  
8 removed in plasma after administration of said compound to a patient such that the extent  
9 and rate of appearance of hydralazine in the plasma is therapeutically similar to that of  
10 hydralazine after administration of hydralazine under similar clinical conditions.

11

12 4. The method of Claims 1, 2 or 3 wherein R<sub>1</sub> and R<sub>2</sub> are independently a branched or  
13 straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted  
14 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,  
15 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form  
16 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon  
17 atoms.

18

19 5. The method of Claims 1, 2 or 3 wherein R<sub>2</sub> is H and R<sub>1</sub> is a branched or straight chain  
20 alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted  
21 or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
22 unsubstituted alkylcycloalkyl, lower alkenyl.

23

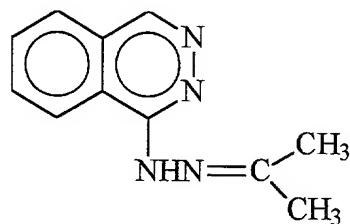
24 6. The method of Claim 4 wherein R<sub>1</sub> and R<sub>2</sub> are a branched or straight chain alkyl having  
25 from about 1 to about 7 carbon atoms.

26

27 7. The method of Claim 5 wherein R<sub>1</sub> is a branched or straight chain alkyl having from  
28 about 1 to about 7 carbon atoms.

1    8. The method of Claim 6 wherein said compound has the formula:

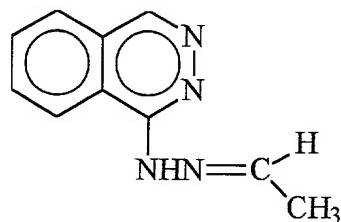
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3

4    9. The method of Claim 7 wherein said compound has the formula:

5

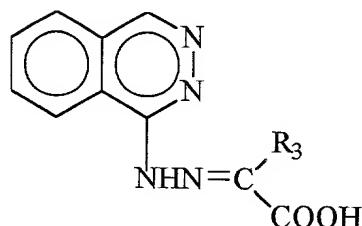


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7

8    10. The method of Claim 1 wherein said compound has the formula:

9



10

11    where R<sub>3</sub> is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,  
12    substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or  
13    unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group  
14    having the formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 1 to about 7.

15

1    11. The method of Claim 10 wherein R<sub>3</sub> is a branched or straight chain alkyl having from  
2    1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted  
3    aralkyl, substituted or unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted  
4    alkylcycloalkyl.

5

6    12. The method of Claim 10 wherein R<sub>3</sub> is a group having the formula (CH<sub>2</sub>)<sub>n</sub>COOH  
7    where n is from 1 to about 7.

8

9    13. The method of Claims 1, 2 or 3 wherein R<sub>1</sub> and R<sub>2</sub> are substituted or unsubstituted  
10    aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,  
11    substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form  
12    part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon  
13    atoms.

14

15    14. The method of Claims 1, 2 or 3 wherein R<sub>2</sub> is H and R<sub>1</sub> is substituted or unsubstituted  
16    aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,  
17    substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form  
18    part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon  
19    atoms.

20

21    15. The method of Claim 13 wherein R<sub>1</sub> and R<sub>2</sub> are substituted or unsubstituted aryl,  
22    substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
23    unsubstituted alkylcycloalkyl, lower alkenyl.

24

25    16. The method of Claim 13 wherein R<sub>1</sub> and R<sub>2</sub> together form part of a substituted or  
26    unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms.

27

1    17. The method of Claim 14 wherein R<sub>2</sub> is H and R<sub>1</sub> is substituted or unsubstituted aryl,  
2    substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
3    unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form part of a  
4    substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms.

5

6    18. The method of Claim 14 wherein R<sub>2</sub> is H and R<sub>1</sub> is substituted or unsubstituted aryl,  
7    substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
8    unsubstituted alkylcycloalkyl, lower alkenyl.

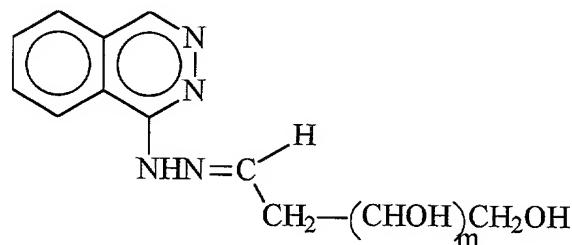
9

10   19. The method of Claims 1,2 or 3 wherein R<sub>2</sub> has the formula CH<sub>2</sub>(CHOH)<sub>m</sub>CH<sub>2</sub>OH  
11   where m is 2 or 3.

12

13   20. The method of Claim 19 wherein said compound has the formula:

14



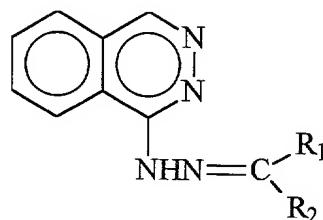
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16   where m is 2 or 3.

17

18   21. A compound having the formula:

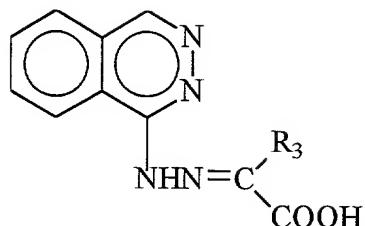
19



1

2 or a compound having the formula:

3



4

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6 where R<sub>1</sub> and R<sub>2</sub> are independently H, branched or straight chain alkyl having from 2 to  
7 about 7 carbon atoms, unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
8 substituted or unsubstituted aralkyl, substituted or unsubstituted alkylcycloalkyl, lower  
9 alkenyl; where R<sub>3</sub> is a branched or straight chain alkyl having from 2 to about 7 carbon  
10 atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted  
11 or unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a  
12 group having the formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 3 to about 7; with the proviso  
13 that when R<sub>1</sub> is H or methyl, then R<sub>2</sub> is a branched or straight chain alkyl having from 2  
14 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted  
15 cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted  
16 alkylcycloalkyl, lower alkenyl.

17

18 22. The compound of Claim 21 wherein R<sub>1</sub> and R<sub>2</sub> are independently a branched or  
19 straight chain alkyl having from 2 to about 7 carbon atoms, substituted or unsubstituted  
20 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,  
21 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form  
22 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon  
23 atoms.

24

1    23. The compound of Claim 21 wherein R<sub>2</sub> is H and R<sub>1</sub> is a branched or straight chain  
2    alkyl having from 2 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted  
3    or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
4    unsubstituted alkylcycloalkyl, lower alkenyl.

5

6    24. The compound of Claim 23 wherein R<sub>1</sub> and R<sub>2</sub> are a branched or straight chain alkyl  
7    having from about 2 to about 7 carbon atoms.

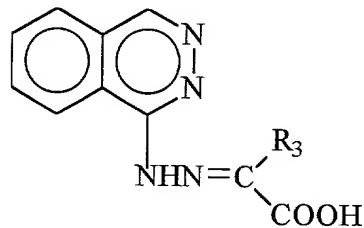
8

9    25. The compound of Claim 23 wherein R<sub>1</sub> is a branched or straight chain alkyl having  
10   from about 2 to about 7 carbon atoms.

11

12   26. The compound of Claim 21 wherein said compound has the formula:

13



14

15   where R<sub>3</sub> is a branched or straight chain alkyl having from 2 to about 7 carbon atoms,  
16   substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or  
17   unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group  
18   having the formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 3 to about 7.

19

20   27. The compound of Claim 26 wherein R<sub>3</sub> is a branched or straight chain alkyl having  
21   from 2 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or  
22   unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, aralkyl, substituted or  
23   unsubstituted alkylcycloalkyl.

24

1    28. The compound of Claim 26 wherein R<sub>3</sub> is a group having the formula (CH<sub>2</sub>)<sub>n</sub>COOH  
2    where n is from 3 to about 7.

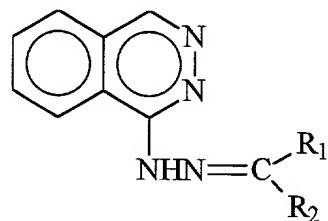
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4    29. The compound of Claim 21 wherein R<sub>1</sub> is substituted or unsubstituted aryl,  
5    substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
6    unsubstituted alkylcycloalkyl.

7

8    30. A particulate-free hydralazine composition comprising compound having the  
9    formula:

10

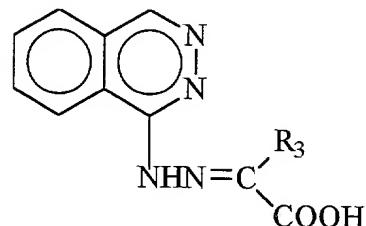


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13    or a compound having the formula:

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16

17    where R<sub>1</sub> and R<sub>2</sub> are independently H, substituted or unsubstituted branched or straight  
18    chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl,  
19    substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or  
20    unsubstituted alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form part of a

1 substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms;  
2 where R<sub>3</sub> is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,  
3 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or  
4 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group  
5 having the formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 1 to about 7 in a pharmaceutically  
6 acceptable salt or diluent.

7 31. The composition of Claim 30 wherein the composition is a liquid pharmaceutical  
8 composition and the composition has been stored from about 18 to about 24 months after  
9 completion of manufacturing and storage was initiated.

10

11 32. The composition of Claim 30 wherein the composition is an injectable formulation  
12 and yellow-green particles do not form from 1 to about 2 months after storage 40° C and  
13 after about 6 months storage at 25° C.

14

15 33. The composition of Claim 31 wherein the average number of particles of about 10  
16 microns in the composition does not exceed 6,000.

17

18 34. The composition of Claim 31 wherein the average number of particles of about 25  
19 microns in the composition does not exceed 600.

20

21 35. The composition of Claim 31 wherein no particles are visible.

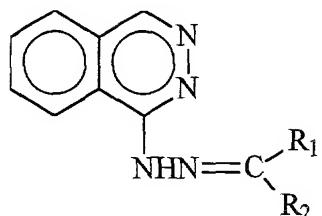
22

23 36. The composition of Claim 31 wherein the average number of particles of about 10  
24 microns in the composition does not exceed 6,000, the average number of particles of  
25 about 25 microns in the composition does not exceed 600, and no particles are visible.

26

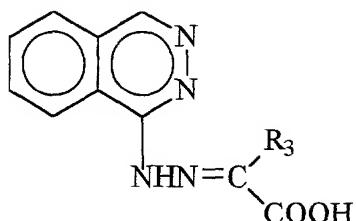
- 1    37. A metal ion-free hydralazine composition comprising a compound having the  
 2    formula:

3



4

- 5    or a compound having the formula:



6

- 7    where R<sub>1</sub> and R<sub>2</sub> are independently H, branched or straight chain alkyl having from 1 to  
 8    about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted  
 9    cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted  
 10   alkylcycloalkyl, lower alkenyl or R<sub>1</sub> and R<sub>2</sub> together form part of a substituted or  
 11   unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms; where R<sub>3</sub> is a  
 12   branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or  
 13   unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted  
 14   cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group having the  
 15   formula (CH<sub>2</sub>)<sub>n</sub>COOH where n is from 1 to about 7; in a pharmaceutically acceptable salt  
 16   or diluent; and wherein said compound in said hydralazine composition does not complex  
 17   with metal ions.

18

- 19    38. The composition of Claim 37 wherein the metal ions are selected from the group  
 20   consisting of Cu<sup>+2</sup>, Fe<sup>+2</sup> and Fe<sup>+3</sup>.

21